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EXAMINER	
GREENE, IVAN A	
ART UNIT	**PAPER NUMBER**
1619	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/553,003	ZEIGERSON, EHUD	
	Examiner	Art Unit	
	IVAN GREENE	1619	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 April 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3 and 5-31* is/are pending in the application.

4a) Of the above claim(s) *16-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3 and 5-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *04/14/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Priority

The U.S. effective filing date for claims 1, 3, 5-13 and 15 has been determined to be 04/10/2003, the filing date of the document 60/461,860. The U.S. effective filing date for claim 14 has been determined to be 04/12/2004 the filing date of the document PCT/US04/11485. The full scope of claim 14 is not supported by the document 60/461,860. No foreign priority has been claimed in the instant application.

Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

1. New grounds of rejection necessitated by amendment: Claims 1, 3, 5-10 and 12-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over WRIGHT (US 6,379,704) in view of LI (US 4,183,681), O'HAGAN (US 2002/0025329), HUBER (US 4,165,219), CROOKS (Journal of the American Chemical Society, Vol. 124, No.

45, pp. 13360-13361) and GODFREY ("Mixing in the Process industries," 2nd ed., Chapter 12 "Static mixers").

Determination of the scope

and content of the prior art (MPEP 2141.01)

WRIGHT teaches a method for preparing microparticles having a selected polymer molecular weight (abstract). WRIGHT further teaches their method comprises the steps of: (a) preparing a first phase, the first phase comprising a nucleophile, a polymer [...] and a solvent for the polymer; (b) *combining the first phase with a second phase under the influence of mixing means to form an emulsion*; (C) combining the emulsion and an extraction medium, thereby forming microparticles [emphasis added] (2:28-35).

WRIGHT teaches the polymers comprising varying lactide:glycolide ratios (3:62-67; 4:1). WRIGHT further teaches example 3 in which the polymer (PLGA MEDISORB® polymers) was dissolved in ethyl acetate to produce a 16.7% w/w polymer solution; the naltrexone active agent was dissolved in benzyl alcohol to produce a 30.0% w/w solution; the polymer and active agent solutions were then mixed together until a single homogenous solution (organic phase) was produced; the aqueous phase contained 1% w/w polyvinyl alcohol and a saturating amount of ethyl acetate; then these two solutions were pumped via positive displacement pumps at a ratio of 3:1 (aqueous: organic) through a 1/4 inch in-line mixer to form an emulsion; and the microparticles were collected on a 25μm sieve and rinsed with a cold (<5˚C) 25% ethanol solution (Example

3, columns 8-9; particularly 8:9-36). WRIGHT teaches *using a Kenics static mixer[1] for mixing the emulsions to form microparticles ranging from about 80-90 µm* (5:52-57). The examiner cites US 5,733,566 column 8, lines 18-47 for a more complete description of the MEDISORB® polymers.

Ascertainment of the difference between

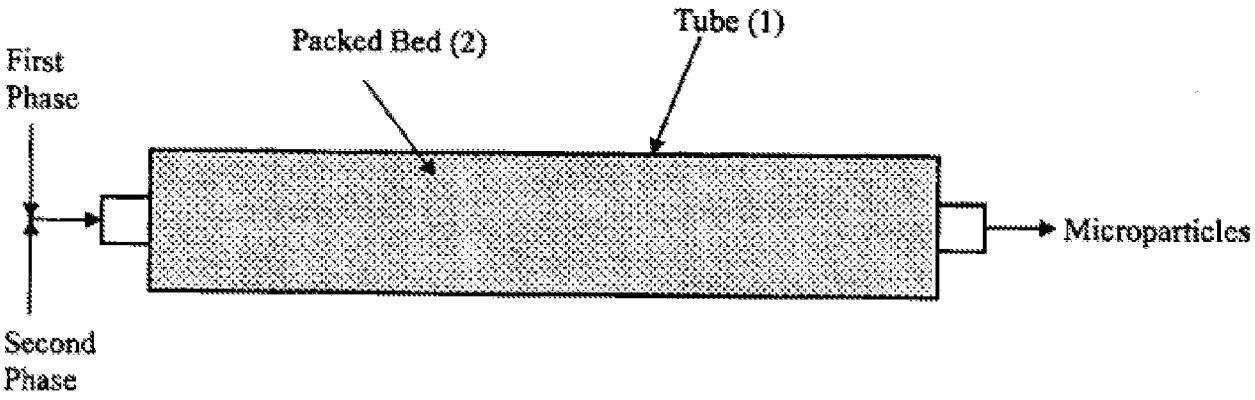
the prior art and the claims (MPEP 2141.02)

The difference between the rejected claims and the teachings of WRIGHT is that WRIGHT does not expressly teach forming an emulsion by passing the phases through a packed bed static mixer under laminar flow conditions; or the packing material is glass beads having a size ranging from 20 µm to 1000 µm. The deficiency in forming an emulsion by passing the phases through a packed bed static mixer is cured by the teachings of LI as detailed below. HUBER teaches glass beads as a column packing material. CROOKS provides motivation to use glass beads as a mixing means under laminar flow conditions. O'HAGAN expressly teaches the use of an emulsion stabilizer in the process of forming PLGA microspheres.

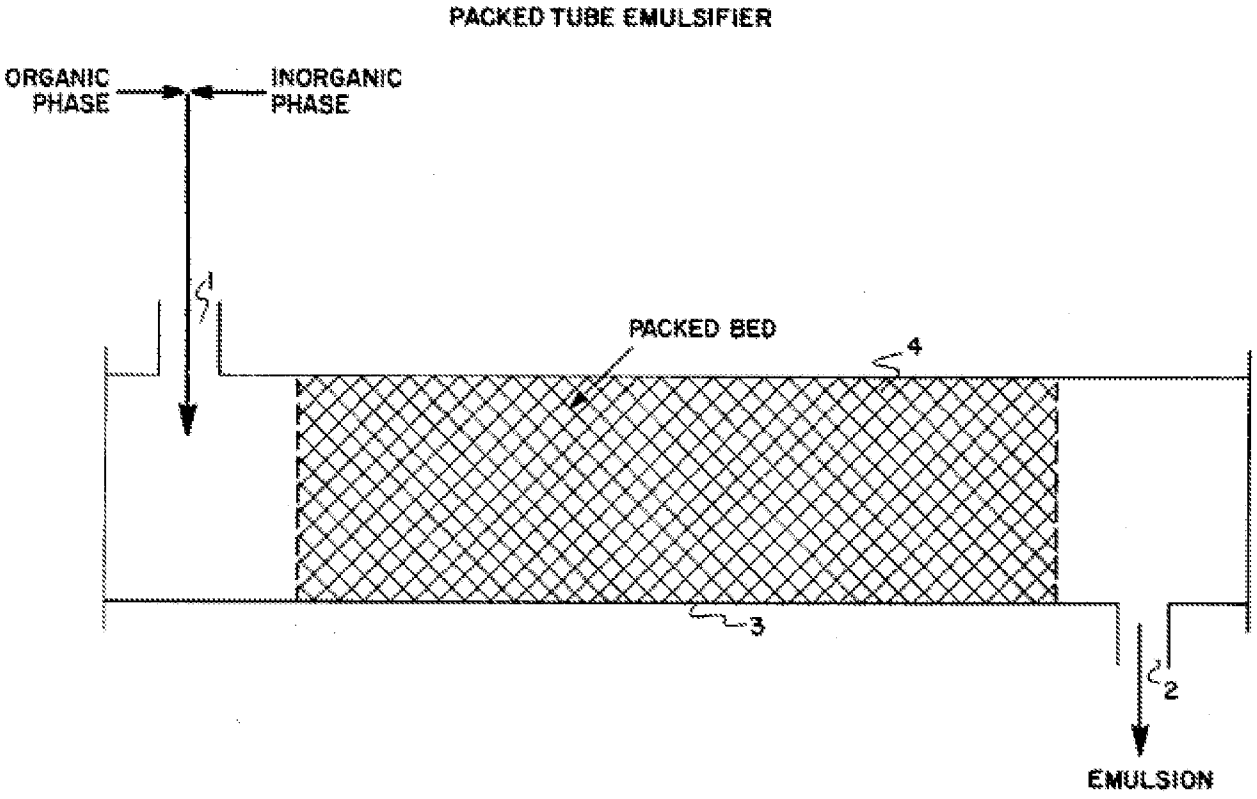
Applicant's specification details the process of forming an emulsion (microparticles) by passing the phases through a packed bed static mixer under laminar flow conditions in figure 1 reproduced below for convenience:

[1] A static mixer is an in-line mixing device consisting of mixing elements inserted in a length of pipe. A Kenics static mixer is distinguished by the mixing elements in the pipe, which consist of a series of short helix of one-and-a-half tube diameter lengths, each element has a twist of 180° and right-hand and left-hand elements are arranged at 90° to one another along the axis of the pipe (see GODFREY: p. 225, lines 1-2; p. 227, paragraph 4; Figure 12.2).

Figure 1 – Packed Bed Apparatus



Li teaches emulsion microparticles (μ-sized droplets) prepared utilizing an emulsification device comprising an enclosure having orifices thereby permitting flow of a fluid through the enclosure along one of its axis which enclosure is packed with a material which causes the flow of fluids to be broken down into many fine streams, which fine streams being in intimate contact one with the other, remix rapidly and repeatedly, resulting in the formation of the desired emulsion (abstract). Li teaches forming an emulsion (microparticles) by passing the phases through a packed bed apparatus in figure 1 reproduced below for convenience:



LI teaches the arrow pointing into the opening indicates the entrance (1) into which the immiscible fluids are simultaneously introduced for passage through the enclosure (3) to the exit (2), indicated by the arrow pointing away from the enclosure (3), fluid flow being through the enclosure in the direction resulting from the indicated mode of fluid introduction; the hatching (4) represents the packing filling the enclosure (1:60-68). LI further teaches suitable packing material is selected from the group consisting of steel metal sponge, *inter alia* (3:12-17). LI further teaches the length of the enclosure from entrance orifices to exit orifices, the amount of packing, the density of the packing, and *the type of packing material packed is left to the practitioner, depending on the type of emulsion desired, the density of the fluids used and the final ratio of internal to external phase desired* (3:35-40). LI further teaches the fluid feed

means are typically selected from the group consisting of pumps for each individual fluid or group of fluids or gravity feed tanks and conduits or syringes for each fluid or group of fluids or any combination of the above (3:43-46). LI further teaches forming different types of emulsions (e.g. water-in-oil, water-in-oil-in-water), and suggests *many variations in the basic theme can be envisioned and all are included in the scope of their invention* (3:49-68). LI further teaches the fluids typically used in preparing a water-oil-water emulsion include an internal water phase wherein is dissolved or suspended any desired material such as medicinal; the oil phase typically comprises and oil component such as petroleum distillate; and the oil phase may contain a surfactant (4:1-9). LI teaches the emulsions prepared by the use of the instant apparatus may have droplet size from 0.1μm to greater than 50 μm (4:33-35).The examiner notes, as currently recited, the microparticles of claim 1 read on the micro-sized droplets of LI because no specific definition for "microparticles" has been provided in the instant specification. And the broadest reasonable interpretation of "microparticles" encompasses micro-sized droplets (see MPEP § 2111 for a discussion of "broadest reasonable interpretation").

Li teaches *the advantage of using the packed tube mixer over the Kenics static mixer is that the packed tube mixer is much more effective in making high ratio emulsions (i.e. particle size 20 μm or more) than Kenics* because of the structure difference between the two devices, that is the packed tube is much more densely packed in a random manner as compared to the Kenics (2:26-28; 5:1-9). Finally, LI teaches mixing two immiscible phases in a packed bed static mixer to form an emulsion with drop sizes which are in the same range as currently claimed.

Regarding the limitation "under laminar flow conditions," LI directly suggest gravity feed tanks as an alternative to pumps, suggesting a lower flow rate[2], and criticizes current emulsification machines as being *too powerful* (abstract; 2:34-44). Therefore, the emulsion mixing process described by LI would have reasonably been under laminar flow conditions.

HUBER teaches a packed column where a sample is mixed with a carrier and a reaction takes place in the column which is filled with an inert, finely divided material, such as glass beads having a diameter from 50 µm to 200 µm (1:32-44, 64-66). HUBER teaches glass beads packed in a column which has a mixing function.

CROOKS teaches a microfluidic system and strategy for mixing solutions which and suggest the use of spherical microbeads as a mixing means under laminar shear flow conditions (p. 13360, col. 1, lines 26-34). CROOKS teaches the interstices between the microbeads provide a simple means for reducing the effective thickness of the fluid laminae, thereby greatly increasing the mixing rate for the fluids (p. 13360, col. 1, lines 19-22).

HUBER and CROOKS show that a packed column of spherical elements functioning as a mixing means are known in the prior art, and that microbeads can function as a mixing means under laminar shear flow conditions. Therefore, a person having ordinary skill in the art would have appreciated that spherical microbeads would have been a suitable mixing means for a static mixer under laminar flow conditions.

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[2] see the discussion below in "Response to Arguments" section regarding the flow rate in relation to laminar flow.

O'HAGAN teaches a process for preparing polymer microparticles, similar to WRIGHT, wherein an emulsion stabilizer, such as polyvinyl alcohol or polyvinyl pyrrolidone is used ([0053]).

Finding of prima facie obviousness

Rationale and Motivation (MPEP 2142-2143)

Therefore, given the teachings above, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to use the packed bed static mixer of LI as a means for forming the emulsion microparticles of WRIGHT because LI suggests that the packed bed static mixer is much more effective in making high ratio emulsions (drop sizes greater than 20 μm) than the Kenics static mixer used by WRIGHT. Further, it would have been obvious to and one of ordinary skill in the art would have been motivated to use the spherical beads of HUBER in the packed bed static mixer of LI because, as suggested by CROOKS, the spherical microbeads would have greatly increased the mixing rate of the fluids under laminar flow conditions.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention because both LI and WRIGHT each use static mixers to produce microparticle emulsions with similar particles sizes. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

2. New grounds of rejection necessitated by amendment: Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over WRIGHT in view of LI, O'HAGAN and HUBER, CROOKS and GODFREY, as applied to claims 1-10 and 12-15 above, and further in view of DONOVAN (US 2002/0028216) and YANAI (US 5,846,562).

Determination of the scope

and content of the prior art (MPEP 2141.01)

WRIGHT teaches a method for preparing a PLGA microparticles emulsion and LI teaches packed tube apparatus for forming an emulsion, and HUBER teaches spherical glass beads as a column packing material, as discussed above. O'HAGAN expressly teaches the use of an emulsion stabilizer but does not teach albumin. The difference between the instantly rejected claim and the teachings of WRIGHT, O'HAGAN and LI is that neither WRIGHT, O'HAGAN or LI teach the protein, albumin, as an emulsion stabilizer. This deficiency in the protein, albumin as an emulsifier is cured by the teachings of YANAI.

YANAI teaches their invention relates to a pharmaceutical composition for oral administration in which a fumagillol derivative is stabilized and exhibits remarkable antiangiogenesis activity in oral administration (abstract). YANAI further teaches the suspension of the present invention comprising the fumagillol derivative oleaginous

base and emulsifier, is generally referred to as lipid micro spheres or lipid nanospheres (11:49-52). YANAI further teaches [their composition may include] an emulsion stabilizer for improving the stability of the emulsifying agent which includes albumin, inter alia (12:21-23; 12:45-48).

DONOVAN teaches their invention relates to an implantable drug delivery system including botulinum toxin ([0001]). DONOVAN further teaches albumin has widely been used to improve the stability of microsphere encapsulated protein ([0074]).

Finding of prima facie obviousness

Rationale and Motivation (MPEP 2142-2143)

The combination of WRIGHT, LI, O'HAGAN and HUBER is discussed above.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to use albumin as the emulsion stabilizer in the process for preparing microparticles described by WRIGHT and/or O'HAGAN because WRIGHT teaches albumin as a suitable emulsion stabilizer. The skilled artisan would have been motivated to use albumin because, as suggested by DONOVAN, the albumin would have improved the stability of microsphere encapsulated protein, thus creating a more valuable product.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to

one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

Response to Arguments:

Applicant's arguments filed 04/14/2010 have been fully considered but they are not persuasive.

Applicant argues that LI does not teach laminar flow conditions (paragraph bridging pages 6 & 7) and that it is generally unexpected to get sufficient mixing so as to form a good emulsion [under] non-turbulent (laminar) flow condition (p. 7, line 11).

First, applicant's assertion that:

> Li does disclose a packed bed apparatus for forming emulsions. However, Li teaches that its packed bed apparatus is operated under turbulent conditions (*i.e.*, not under laminar flow conditions as is recited in the claims).

(p. 6, paragraph 6), is acknowledged. However, *the words "turbulent conditions" do not appear in the LI reference.* And applicant's assertion, as underlined above, is supported by neither evidence nor scientific reasoning. Applicant is simply asserting that flow rates listed in the tables II, III, VII, and VIII of LI are "very high" without any supporting scientific reasoning or evidence that those flow rates lead to turbulent conditions. Thus, this argument is unconvincing.

The facts are as follows: (1) LI does not expressly teach laminar or turbulent flow conditions; (2) the flow conditions in a static mixer are either laminar or turbulent based upon the Reynolds number of the fluid(s) flowing in the mixer (the Reynolds number is a function of the flow rate, the diameter of the pipe, the density and the viscosity of the fluid); (3) laminar flow conditions occur at low flow rates, and as the flow rate increase a transition from laminar to turbulent will occur[3]; and (4) the Reynolds number depends on the fluid viscosity which, under the conditions of emulsion formation, increases as the emulsion is formed[4].

It remains the examiner's position that, while LI does not disclose the mixing as either turbulent or laminar, LI suggests that the mixing is under laminar flow conditions. LI directly suggest gravity feed tanks as an alternative to pumps, suggesting a lower flow rate, and criticizes current emulsification machines as being *too powerful* (abstract; 2:34-44). Finally, LI teaches mixing two immiscible phases in a packed bed static mixer to form an emulsion with drop sizes which are in the same range as currently claimed. Therefore, the emulsion mixing process described by LI would have reasonably been under laminar flow conditions.

Applicant's argument that it is generally unexpected to get sufficient mixing so as to form a good emulsion [under] non-turbulent (laminar) flow condition (p. 7, line 11), is acknowledged. The examiner respectfully disagrees. The purpose of the static mixer is to facilitate the intermixing of the two different immiscible phases. GODFREY teaches that static mixers were developed with "laminar flow blending operations in mind" (p.

[3] see Robert L. Mott, "Applied Fluid Mechanics" page 175 § 6-7.

234, § 12.2.2). GODFREY further teaches "[l]aminar shear dispersion is required in particular mixing applications where the ultimate size of the particles or drops of a dispersed phase is to be reduced in the mixing process" (p. 229, last paragraph). And CROOKS teaches microbeads as a mixing means under laminar shear flow conditions (p. 13360, col. 1, lines 26-34). Therefore, it would not have been unexpected to achieve sufficient mixing, under laminar flow conditions, to form a good emulsion.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. MOHR (Industrial and Engineering Chemistry, Vol. 49, No. 11, pp. 1855 & 1856) is cited as a general discussion of mixing under laminar flow conditions which is a limitation of the instantly claimed invention. MAA (Journal of Microencapsulation, Vol. 13, No. 4, pp. 419-433) is cited as a teaching of the use of static mixers to produce PLGA microparticles. The difference between MAA and the instantly claimed invention is that MAA does not suggest the use of a packed column type static mixer.

Claims 1, 3 and 5-15 have been examined on the merits. Claims 1, 3 and 5-15 are rejected under U.S.C. § 103(a). No claims allowed at this time.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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[4] see U.S. 6,369,121 column, 10, lines 37-49.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to IVAN GREENE whose telephone number is (571)270-5868. The examiner can normally be reached on Monday through Thursday 7AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bonnie Eyler can be reached on (571) 272-0871. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/YVONNE L. EYLER/
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